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The Crystal and Molecular Structure of the 2:1 Molecular Complex of Theophylline with Phenobarbital

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(*Received* 23 *August* 1976; *accepted* 15 *October* 1976)

The 2:1 molecular complex of theophylline with phenobarbital crystallizes in the orthorhombic space group *Pnma*, with the unit-cell dimensions $a = 6\cdot991\ (5)$, $b = 25\cdot554\ (17)$, $c = 15\cdot129\ (7)$ Å. The approximate structure in the space group $Pn2_1a$ was initially solved by the application of *MULTAN*. The correct structure was then refined in *Pnma* to give a final R index of 0·095. The phenobarbital molecule has mirror symmetry and participates in weak N—H···N hydrogen bonds to two symmetrically related theophylline molecules. The N(7) atom of theophylline forms a hydrogen bond with the O(2) atom of the adjacent theophylline molecule, and the C(8) atom of theophylline may form a weak C—H···O hydrogen bond with the O(4) atom of the adjacent phenobarbital.

Introduction

Xanthines and barbiturates form crystalline complexes with a variety of other molecular series as well as with each other. In fact, theophylline and phenobarbital form a molecular complex (Higgins & Dunker, 1944; Bender & Nelson, 1973) with a 2:1 molar ratio, similar to the complex of phenobarbital with 8-bromo-9-ethyladenine (Kim & Rich, 1968). However, the modes of hydrogen bonding in these two complexes seem to be distinct: the ring N(1) atom of theophylline is unable to participate in a hydrogen bond, while the N(1) atom of adenine may take part in the hydrogen-bond formation (see Fig. 1). Phenobarbital (a derivative of uracil) is physiologically used as a sedative hypnotic agent, while theophylline (a derivative of xanthine) is effective as a diuretic and cardiac stimulant; these two drugs are frequently used at the same time. To explore the possibility that the specific interaction between phenobarbital and theophylline may play a significant role in the multiple pharmacological effect of these drugs, the crystal structure analysis of the 2:1 molecular complex of theophylline with phenobarbital was carried out, and the mode of the specific hydrogen bonding was elucidated.

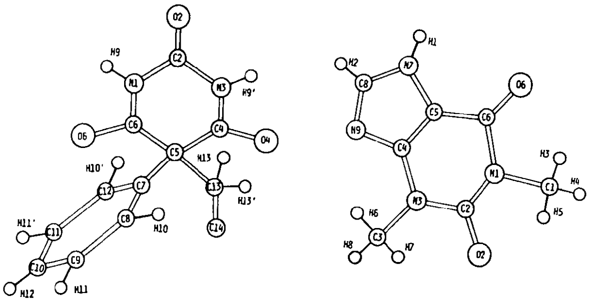

Fig. 1. Theophylline and phenobarbital (atomic numbering).

Experimental

Colourless needles were obtained by distillation of a 50% aqueous ethanol solution of theophylline and phenobarbital in a 2:1 molar ratio under reduced pressure. The unit-cell dimensions were initially obtained from precession photographs and refined by a diffractometer: $a = 6\cdot991\ (5)$, $b = 25\cdot554\ (17)$, $c = 15\cdot129\ (7)$ Å. The density (measured by the flotation method) is 1·459 g cm^{-3}, which is in good agreement with that calculated for four units of two theophylline and one phenobarbital in a unit cell. The observed extinctions, 0*kl* when *k* + *l* is odd and *hk*0 when *h* is odd, indicate the space group to be either *Pn*2$_1$*a* or *Pnma*; the latter, containing one-half of the 2:1 complex in an asymmetric unit, was confirmed to be correct. Some crystal data are listed in Table 1.

The intensity data were collected on an automatic four-circle Rigaku Denki diffractometer with Cu $K\alpha$ radiation and the ω–2θ scan technique. Three standard reflexions were measured every 40 reflexions and their intensities showed no unusual fluctuation or decay during the run. 1830 independent reflexions were measured and consequently corrected for Lorentz and polarization factors, but no correction for absorption was made. The structure factors were normalized to an absolute scale by the usual Wilson method.

Table 1. *Crystal data for the theophylline–phenobarbital complex*

Chemical formula $C_7H_8N_4O_2.\frac{1}{2}C_{12}H_{12}N_2O_3$
FW 296·3
Orthorhombic, space group *Pnma*

$a = 6{\cdot}991 \pm 0{\cdot}005$ Å
$b = 25{\cdot}554 + 0{\cdot}017$
$c = 15{\cdot}129 \pm 0{\cdot}007$
$V = 2702{\cdot}8$ Å^3
$Z = 8$
$D_m = 1{\cdot}459$ g cm^{-3}
$D_x = 1{\cdot}459$

Table 2. *Final atomic parameters with estimated standard deviations in parentheses.*

All quantities for non-hydrogen atoms are $\times 10^4$. All coordinates for hydrogen atoms are $\times 10^3$.
The form of the anisotropic ellipsoid is $\exp[-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl)]$.

Theophylline

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N(1)	1917 (8)	5457 (2)	3440 (3)	161 (14)	11 (1)	31 (3)	1 (7)	8 (11)	−1 (3)
C(2)	2246 (10)	5142 (3)	4164 (4)	164 (17)	10 (1)	35 (3)	−1 (8)	−2 (13)	−5 (3)
N(3)	2766 (8)	4631 (2)	4000 (3)	168 (14)	12 (1)	22 (3)	7 (6)	−2 (10)	2 (3)
C(4)	2969 (10)	4463 (3)	3152 (4)	125 (16)	12 (1)	24 (3)	−4 (8)	−7 (12)	5 (3)
C(5)	2619 (9)	4784 (2)	2450 (5)	123 (15)	9 (1)	33 (3)	4 (7)	7 (13)	−2 (4)
C(6)	2065 (10)	5309 (2)	2544 (5)	139 (16)	12 (1)	35 (3)	−14 (7)	18 (13)	−1 (4)
N(7)	2976 (8)	4487 (2)	1698 (3)	124 (13)	12 (1)	31 (3)	−4 (6)	−3 (10)	−3 (3)
C(8)	3497 (10)	4007 (3)	2000 (4)	134 (17)	14 (1)	32 (3)	1 (8)	−21 (13)	−4 (4)
N(9)	3527 (8)	3974 (2)	2882 (3)	148 (14)	12 (1)	29 (3)	13 (6)	−13 (10)	−4 (3)
C(1)	1370 (13)	6010 (3)	3640 (5)	341 (26)	10 (1)	44 (3)	24 (10)	−10 (17)	−8 (4)
O(2)	2084 (8)	5311 (2)	4909 (3)	320 (16)	16 (1)	32 (2)	5 (7)	−2 (11)	−17 (3)
C(3)	3081 (13)	4272 (3)	4746 (4)	333 (26)	16 (1)	26 (3)	46 (11)	22 (16)	12 (4)
O(6)	1711 (8)	5626 (2)	1949 (3)	277 (15)	14 (1)	34 (2)	6 (6)	−14 (10)	8 (3)

Phenobarbital

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N(1)	4707 (8)	2040 (2)	3658 (3)	117 (12)	10 (1)	31 (3)	2 (6)	−12 (10)	−1 (3)
C(2)*	4059 (13)	2500	3280 (6)	88 (21)	15 (2)	28 (5)	0	−6 (17)	0
O(2)*	2982 (10)	2500	2656 (5)	170 (18)	20 (1)	45 (4)	0	−75 (15)	0
C(4)	5984 (9)	2989 (3)	4335 (4)	90 (14)	12 (1)	29 (3)	2 (7)	31 (12)	−2 (3)
O(4)	6747 (7)	3400 (2)	4523 (3)	199 (13)	11 (1)	35 (2)	−43 (6)	−8 (9)	5 (2)
C(5)*	6283 (13)	2500	4884 (6)	83 (20)	12 (2)	23 (4)	0	−27 (16)	0
C(7)*	4825 (13)	2500	5637 (6)	78 (20)	10 (2)	23 (4)	0	−9 (16)	0
C(8)	4160 (10)	2966 (3)	5992 (4)	154 (17)	12 (1)	30 (3)	8 (8)	−15 (13)	−4 (3)
C(9)	2838 (11)	2971 (3)	6684 (5)	143 (17)	17 (1)	47 (4)	25 (9)	6 (15)	2 (4)
C(10)*	2175 (15)	2500	7019 (6)	132 (25)	28 (3)	20 (5)	0	22 (18)	0
C(13)*	8373 (14)	2500	5274 (6)	99 (22)	21 (2)	27 (5)	0	−49 (17)	0
C(14)*	9936 (16)	2500	4561 (8)	86 (24)	31 (3)	55 (7)	0	35 (22)	0

Theophylline

	x	y	z	B_0 (Å^2)
H(1)[N(7)]	267 (13)	461 (3)	102 (5)	5 (2)
H(2)[C(8)]	388 (11)	367 (3)	153 (5)	3 (2)
H(3)[C(1)]	201 (13)	625 (3)	324 (5)	5 (2)
H(4)[C(1)]	188 (14)	615 (3)	422 (6)	5 (2)
H(5)[C(1)]	26 (13)	608 (3)	317 (5)	5 (2)
H(6)[C(3)]	452 (13)	407 (3)	467 (5)	5 (2)
H(7)[C(3)]	296 (14)	386 (3)	464 (6)	6 (2)
H(8)[C(3)]	191 (14)	435 (3)	524 (6)	6 (2)

Phenobarbital

	x	y	z	B_0 (Å^2)
H(9)[N(1)]	425 (13)	172 (3)	334 (6)	6 (2)
H(10)[C(8)]	466 (13)	335 (3)	575 (5)	3 (2)
H(11)[C(9)]	250 (12)	333 (3)	699 (5)	2 (2)
H(12)[C(10)]	138 (16)	250	753 (8)	3 (2)
H(13)[C(13)]	866 (12)	279 (3)	569 (5)	4 (3)

* The parameters B_{12}, B_{23}, of the atoms with $y = 0{\cdot}25$ are equal to zero by symmetry.

Structure determination and refinement

The first approximate structure in the space group $Pn2_1a$ was solved with the multisolution tangent-formula procedure *MULTAN* (Germain, Main & Woolfson, 1971). In the first *E* map all the non-hydrogen atoms, except two atoms of the ethyl group in phenobarbital, were located. After refinement it was suggested that the phenobarbital molecule itself may possess a mirror plane through seven atoms [C(2), O(2) and C(5) of the oxopyrimidine moiety, C(7) and C(10) of the benzene ring and the ethyl C atoms, C(13) and C(14)]. Therefore, the correct space group should be *Pnma*. In fact, the following Fourier calculation in the space group *Pnma* revealed the positions of the remaining two ethyl C atoms on the mirror plane. Four cycles of the full-matrix least-squares refinement with isotropic temperature factors reduced the *R* index to 0·137. Further refinement with block-diagonal least squares with anisotropic temperature factors for all the non-hydrogen atoms gave an *R* index of 0·115. At this point a difference Fourier map was calculated, and all the H atoms, excluding the three of the terminal methyl group in the phenobarbital molecule, were found. Three more cycles of the final refinement including H atoms with isotropic temperature factors were carried out and the *R* index was reduced finally to 0·095. Final atomic parameters with their estimated standard deviations are listed in Table 2.*

Table 3. *Bond lengths* (Å) *and bond angles* (°) *with standard deviations in parentheses*

Theophylline

N(1)–C(2)	1·379 (9)	N(7)–C(8)	1·360 (9)
C(2)–N(3)	1·377 (9)	C(8)–N(9)	1·337 (9)
N(3)–C(4)	1·361 (9)	C(4)–N(9)	1·371 (9)
C(4)–C(5)	1·365 (10)	N(7)–H(1)	1·09 (9)
C(5)–C(6)	1·402 (10)	C(8)–H(2)	1·15 (8)
N(1)–C(6)	1·413 (9)	C(1)–H(3)	0·97 (9)
N(1)–C(1)	1·495 (11)	C(1)–H(4)	1·01 (9)
C(2)–O(2)	1·211 (9)	C(1)–H(5)	1·07 (9)
N(3)–C(3)	1·473 (11)	C(3)–H(6)	1·14 (9)
C(6)–O(6)	1·236 (9)	C(3)–H(7)	1·07 (9)
C(5)–N(7)	1·390 (9)	C(3)–H(8)	1·12 (10)

C(6)–N(1)–C(2)	126·5 (6)	N(7)–C(5)–C(6)	130·9 (7)
C(1)–N(1)–C(2)	115·7 (6)	N(7)–C(5)–C(4)	106·0 (6)
C(1)–N(1)–C(6)	117·8 (6)	C(5)–C(6)–N(1)	112·0 (6)
N(1)–C(2)–N(3)	117·0 (6)	O(6)–C(6)–N(1)	120·6 (7)
O(2)–C(2)–N(3)	122·1 (7)	O(6)–C(6)–C(5)	127·5 (7)
O(2)–C(2)–N(1)	120·9 (7)	C(5)–N(7)–C(8)	105·4 (6)
C(2)–N(3)–C(4)	119·9 (6)	H(1)–N(7)–C(8)	129 (5)
C(3)–N(3)–C(4)	120·6 (6)	H(1)–N(7)–C(5)	125 (5)
C(3)–N(3)–C(2)	119·5 (6)	N(7)–C(8)–N(9)	113·4 (6)
N(3)–C(4)–C(5)	121·6 (6)	H(2)–C(8)–N(9)	125 (4)
N(9)–C(4)–C(5)	111·6 (6)	H(2)–C(8)–N(7)	122 (4)
N(9)–C(4)–N(3)	126·8 (6)	C(8)–N(9)–C(4)	103·6 (6)
C(4)–C(5)–C(6)	123·1 (7)		

Phenobarbital

N(1)–C(2)	1·384 (11)	C(9)–C(10)	1·385 (13)
N(1)–C(6)	1·361 (8)	C(5)–C(13)	1·576 (13)
C(5)–C(6)	1·516 (11)	C(13)–C(14)	1·536 (15)
C(2)–O(2)	1·207 (12)	N(1)–H(9)	1·00 (9)
C(4)–O(4)	1·212 (8)	C(8)–H(10)	1·10 (8)
C(5)–C(7)	1·528 (12)	C(9)–H(11)	1·05 (8)
C(7)–C(8)	1·386 (11)	C(10)–H(12)	0·96 (12)
C(8)–C(9)	1·397 (10)	C(13)–H(13)	1·00 (8)

C(6)–N(1)–C(2)	124·9 (6)	C(5)–C(7)–C(8)	120·8 (7)
H(9)–N(1)–C(2)	112 (5)	C(12)–C(7)–C(8)	118·4 (7)
H(9)–N(1)–C(6)	122 (5)	C(7)–C(8)–C(9)	121·3 (7)
N(1)–C(2)–N(3)	116·4 (7)	H(10)–C(8)–C(9)	117 (4)
O(2)–C(2)–N(1)	121·8 (8)	H(10)–C(8)–C(7)	121 (4)
C(5)–C(6)–N(1)	117·3 (6)	C(8)–C(9)–C(10)	119·2 (8)
O(6)–C(6)–N(1)	120·9 (6)	H(11)–C(9)–C(10)	121 (5)
O(6)–C(6)–C(5)	121·7 (6)	H(11)–C(9)–C(8)	119 (4)
C(4)–C(5)–C(6)	111·2 (7)	C(9)–C(10)–C(11)	120·5 (9)
C(6)–C(5)–C(7)	108·4 (7)	H(12)–C(10)–C(11)	120 (7)
C(6)–C(5)–C(13)	109·5 (7)	H(13)–C(13)–C(14)	108 (5)
C(7)–C(5)–C(13)	109·9 (7)	H(13)–C(13)–C(5)	115 (5)
C(5)–C(13)–C(14)	113·4 (8)		

Table 4. *Deviations* (Å) *of the atoms from some least-squares planes, and the dihedral angles between the planes*

An asterisk denotes the atoms used in the plane calculation.

(*a*) Theophylline

Plane 1: $-0·9607x - 0·2777y - 0·0067z + 5·1926 = 0·0$
Plane 2: $-0·9611x - 0·2763y - 0·0012z + 5·1436 = 0·0$
Plane 3: $-0·9560x - 0·2932y - 0·0086z + 5·3693 = 0·0$

	Plane 1	Plane 2	Plane 3
N(1)	–0·002*	–0·003*	–0·045
C(2)	–0·006*	–0·003*	–0·039
N(3)	0·009*	0·009*	–0·001
C(4)	0·000*	–0·008*	0·000*
C(5)	0·014*	0·002*	0·002*
C(6)	0·013*	0·004*	–0·021
N(7)	–0·007*	–0·027	–0·004*
C(8)	–0·019*	–0·038	0·004*
N(9)	–0·025*	–0·036	–0·003*
C(1)	–0·029*	–0·026	–0·097
O(2)	–0·025*	–0·015	–0·067
C(3)	0·045*	0·049	0·048
O(6)	0·032*	0·019	–0·015

∠ (plane 2)–(plane 3) 1·1°.

(*b*) Phenobarbital

Plane 4: $0·7606x - 0·0000y - 0·6492z + 1·0822 = 0·0$

N(1)	–0·011*	C(4)	0·003*	C(7)	–1·892
C(2)	0·016*	C(5)	–0·377	C(13)	0·351
N(3)	–0·011*	C(6)	0·003*		

Plane 5: $-0·7489x - 0·0000y - 0·6627z + 8·1827 = 0·0$

C(7)	0·005*	C(10)	0·007*	C(12)	–0·002*
C(8)	–0·002*	C(11)	–0·004*	C(5)	–0·004
C(9)	–0·004*				

∠ (plane 4)–(plane 5) 98·0°.

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32241 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

The *UNICS* (1973) system was used in the refinement of the structure. Atomic scattering factors for all atoms were taken from *International Tables for X-ray Crystallography* (1962), and all the computations were carried out on the NEAC 2200-700 computer at this University.

Results and discussion

The final bond lengths and bond angles, and the atomic numbering are shown in Table 3 and Fig. 1 respectively.

Phenobarbital

C(5) of phenobarbital is 0·38 Å out of the oxopyrimidine least-squares plane towards the phenyl group; similar puckering conformations in barbiturates were also observed in the crystalline complexes phenobarbital – 8-bromo-9-ethyladenine (Kim & Rich, 1968) and alloxan – 9-ethyladenine (Shieh & Voet, 1975). This phenomenon has not been detected for several other barbiturates involved in molecular complexes, *e.g.* 5-isopropyl-5-bromoallylbarbituric acid – 9-ethyladenine (Voet & Rich, 1972), barbituric acid – 9-ethyladenine (Voet, 1971, 1972) and barbital – caffeine (Craven & Gartland, 1974). Three independent barbiturate anions, each having different ring conformations, were observed in the crystal of potassium 5-ethylbarbiturate (Gartland, Gatehouse & Craven, 1975). Such puckerings may be due to the nature of the substituents at the 5 and 5′ positions and/or the variety of packing forces in the crystal. It is hard to explain why the C(13)–C(14) bond of the ethyl group (1·64 Å) is significantly longer than the normal C–C single bond. The peak corresponding to C(14), broadened on either side of the mirror plane, was found in the Fourier map, but the three H atoms attached to C(14) could not be detected in this map.

Theophylline

The crystal structures of the following theophylline-related compounds have so far been reported: theophylline (Sutor, 1958), *cis* and *trans*-theo-

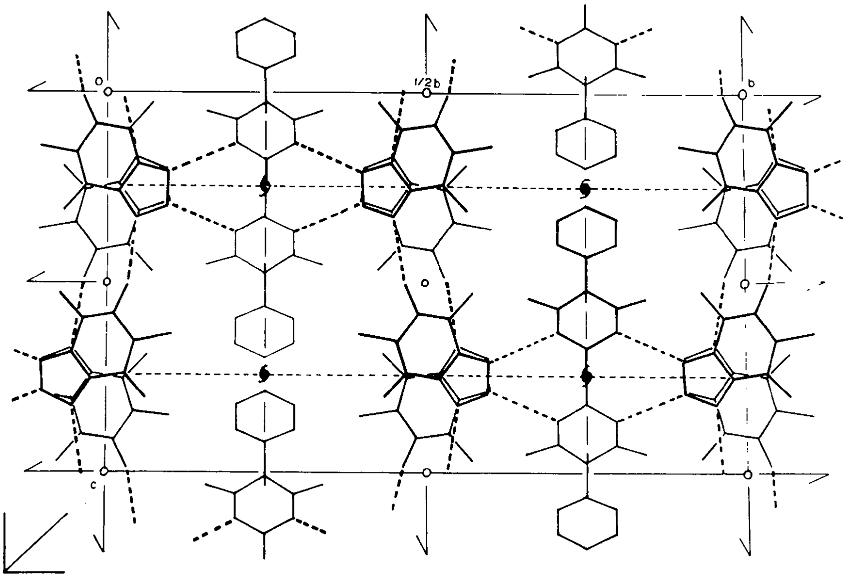

Fig. 2. The crystal packing of the theophylline–phenobarbital complex viewed along **a**.

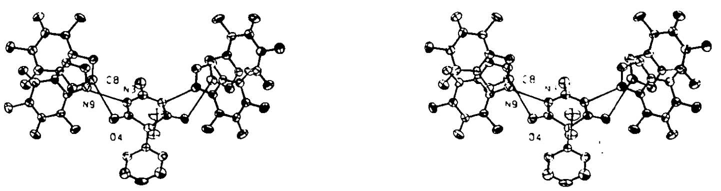

Fig. 3. Stereo projection of the molecular complex of theophylline with phenobarbital. Open bonds represent the hydrogen-bonding contacts.

Table 5. *Hydrogen bonds and short van der Waals contacts, with standard deviations in parentheses*

(*a*) Hydrogen bonds (X–H $\cdots$ Y)

			Distance (Å)			Angle (°)
X	H	Y	X–H	$X\cdots Y$	H$\cdots Y$	X–H$\cdots Y$
N(7)$_a^T$	H(1)$_a^T$	O(2)$_b^T$	1·09 (9)	2·756 (8)	1·70 (9)	160 (8)
N(1)$_c^P$	H(9)$_c^P$	N(9)$_a^T$	1·00 (8)	2·961 (8)	1·98 (9)	170 (8)
C(8)$_a^T$	H(2)$_a^T$	O(4)$_d^P$	1·15 (8)	3·034 (9)	2·29 (8)	120 (5)

(*b*) Short contacts ($X\cdots Y$)

		Distance (Å)			Distance (Å)			Distance (Å)
X	Y	$X\cdots Y$	X	Y	$X\cdots Y$	X	Y	$X\cdots Y$
O(4)$_a^P$	C(3)$_a^T$	3·412 (11)	C(8)$_a^T$	C(5)$_g^T$	3·599 (10)	C(4)$_a^T$	N(7)$_g^T$	3·508 (9)
N(7)$_a^T$	O(4)$_d^P$	3·445 (8)	N(9)$_a^T$	N(7)$_g^T$	3·436 (8)	C(5)$_a^T$	C(6)$_g^T$	3·385 (10)
C(14)$_a^P$	O(2)$_e^P$	3·583 (14)	O(6)$_a^T$	C(1)$_g^T$	3·517 (11)	C(6)$_a^T$	O(6)$_g^T$	3·435 (9)
O(2)$_a^T$	O(4)$_f^P$	3·500 (8)	C(2)$_a^P$	O(2)$_g^P$	3·087 (12)	N(7)$_a^T$	C(4)$_g^T$	3·499 (9)
C(4)$_a^T$	C(5)$_g^T$	3·474 (10)	O(2)$_a^P$	O(2)$_g^P$	3·527 (15)	C(8)$_a^T$	C(4)$_g^T$	3·345 (10)
C(5)$_a^T$	C(5)$_g^T$	3·499 (14)	O(6)$_a^T$	C(3)$_b^T$	3·346 (11)	N(9)$_a^T$	C(5)$_g^T$	3·568 (9)
C(6)$_a^T$	C(6)$_g^T$	3·498 (15)	C(14)$_a^P$	C(2)$_e^P$	3·373 (15)	N(9)$_a^T$	C(8)$_g^T$	3·480 (9)
N(7)$_a^T$	N(3)$_g^T$	3·530 (8)	C(1)$_a^T$	O(4)$_f^P$	3·425 (11)	N(1)$_a^P$	O(2)$_g^P$	3·253 (9)
N(7)$_a^T$	C(5)$_g^T$	3·574 (9)	N(1)$_a^T$	O(6)$_g^T$	3·430 (8)	C(4)$_a^P$	O(2)$_g^P$	3·548 (10)

The superscripts T, P refer to the molecules theophylline and phenobarbital. The symmetry operations implied by the subscripts are the following:

(*a*) x,y,z
(*b*) $0{\cdot}5-x, 1{\cdot}0-y, -0{\cdot}5+z$
(*c*) $x, 0{\cdot}5-y, z$
(*d*) $-0{\cdot}5+x, y, 0{\cdot}5-z$
(*e*) $1{\cdot}0+x, y, z$
(*f*) $1{\cdot}0-x, 1{\cdot}0-y, 1{\cdot}0-z$
(*g*) $0{\cdot}5+x, y, 0{\cdot}5-z$

phyllinatochlorobis(ethylenediamine)cobalt(III) perchlorate (Kistenmacher & Szalda, 1975; Kistenmacher, 1975), and theophylline – 5-chlorosalicylic acid (Shefter, 1969). The C(2)–N(3) and C(4)–N(9) bond lengths (1·38 and 1·37 Å) seem to be slightly longer than the average values of 1·35 and 1·34 Å found for the comparable bonds in other related compounds. The maximum deviation of an atom from the best plane of the purine ring is 0·049 Å for the methyl C(3), as shown in Table 4.

A similar atomic displacement is reported for the theophylline molecule in the cobalt(III) complex with ethylenediamine. The deviation of C(3) may be due to the repulsion between this atom and O(4) of the phenobarbital molecule connected to theophylline by a N–H $\cdots$ N hydrogen bond.

Molecular packing and the intermolecular hydrogen bond

The molecular packing and hydrogen bonding of this complex viewed along **a** is shown in Fig. 2, in which the dashed lines indicate hydrogen bonds.

The phenobarbital molecule itself possesses exact mirror symmetry. A phenobarbital molecule has two symmetrically related N–H $\cdots$ N bonds with two adjacent theophylline molecules. Such a mode of hydrogen bonding is quite distinct from the cyclic hydrogen-bonded base pairing found in many complexes of barbiturate with adenine or xanthine derivatives. Theophylline molecules associate *via* N(7)–H $\cdots$ O(2) hydrogen bonds nearly parallel to **c**. It is known that the C(8)–H group is more acidic than the C(2)–H group in the purine derivatives, and the observed short contact between the H atom attached to the C(8) of theophylline and the O(4) of phenobarbital (2·29 Å) may support the additional weak C–H $\cdots$ O hydrogen-bond formation, similar to that found in the complex of barbital with caffeine (Craven & Gartland, 1974) (Fig. 3).

The imidazole moieties of the theophylline molecules are stacked in the **a** direction with a stacking distance of 3·48–3·50 Å. The distance between the carbonyl groups of adjacent phenobarbital molecules related by the *a*-glide symmetry operation is short, as shown in Table 5; this contact might be attributed to a dipole–dipole interaction (Bolton, 1964). It might be important in the multiple pharmacological effect that each phenobarbital molecule is surrounded by four theophylline molecules with N–H···N and C–H···O hydrogen bonds.

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The Crystal Structure of $(-)_{589}$-Oxalatobis(ethylenediamine)cobalt(III) $(+)_{589}$-Dicyanomalonatodiamminecobaltate(III) Trihydrate

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(*Received* 21 *September* 1976; *accepted* 13 *October* 1976)

$(-)_{589}$-[Co(ox)(en)$_2$] $(+)_{589}$-[Co(CN)$_2$(mal)(NH$_3$)$_2$].3H$_2$O crystallizes in the orthorhombic space group $P2_12_12_1$ with $a = 16{\cdot}709$ (1), $b = 18{\cdot}139$ (1), $c = 7{\cdot}569$ (1) Å and $Z = 4$. The structure was refined by least-squares calculations to give an R value of 0·034 for 3304 observed amplitudes. The complex anion is a *cis–cis* isomer: a Co atom is surrounded nearly octahedrally by two C atoms of cyano groups, two N atoms of ammonia molecules, both in *cis* positions, and two O atoms of a malonato group. The absolute configuration of the complex anion, $(+)_{589}$-[Co(CN)$_2$(mal)(NH$_3$)$_2$]$^-$, can be designated as Δ, provided that the chirality is defined by the line joining the two C atoms of the cyano groups and that joining the two N atoms of the ammonia molecules. During the data collection, some strong reflexions with low diffraction angles strikingly increased their intensities. The increase in intensity may be ascribed to a change in the extinction effect under X-irradiation.

Introduction

Seven optically active complexes of Co$^{\rm III}$ were isolated whose optical activity arises from the chiral configuration of monodentates coordinated to the central Co atom (Ito & Shibata, 1976). The absolute configuration of the complex ion is of particular importance since no empirical relation between the circular dichroism spectra and the absolute configuration of such complexes has been established. The absolute configuration of one of these complexes, $(-)_{589}$-[Co(NO$_2$)$_2$(ox)(NH$_3$)$_2$]$^-$, was determined by X-ray methods (Shintani, Sato & Saito, 1976). In this paper, the absolute configuration of the title compound will be described.

Experimental

Crystals of $(-)_{589}$-[Co(ox)(en)$_2$] $(+)_{589}$-[Co(CN)$_2$(mal)(NH$_3$)$_2$].3H$_2$O were kindly supplied by Professor M. Shibata of Kanazawa University. They are orange-red square prisms. Unit-cell dimensions were determined from Weissenberg photographs and refined on a diffractometer. The intensities of the reflexions were